**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Applicant(s): Robert MARTUZA *et al.*

Title: **REPLICATION-COMPETENT HERPES SIMPLEX VIRUS MEDIATES DESTRUCTION OF NEOPLASTIC CELLS**

Appl. No.: 10/788,410

Filing Date: 3/1/2004

Examiner: SHEN, Wu Cheng Winston

Art Unit: 1632

Conf. No.: 4953

## BRIEF ON APPEAL

**MAIL STOP APPEAL BRIEF - PATENTS**
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Sir:

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## REAL PARTY IN INTEREST

The real party in interest in this appeal is Georgetown University, which is the assignee of the present application as recorded at Reel/Frame number 007672/0367 and 007921/0475.

## RELATED APPEALS AND INTERFERENCES

No related interferences are pending. An appeal is pending in a commonly owned application, serial No. 11/097,391, which also is directed to a HSV vector.

## STATUS OF CLAIMS

Claims 1-15, 17 and 21-27 are canceled. Claims 16, 18-20 and 28-32 are pending.

Claims 16, 18-20 and 28-32 are at least twice rejected and are the subject of this appeal. The pending claims are presented in Appendix A of this brief.

## STATUS OF AMENDMENTS

No claim amendment was made in the reply accompanying a Request for Continued Examination filed on April 12, 2010. No other amendments or submissions are pending in the application.

## SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of claim 16, the only independent claim on appeal, is reproduced below, with relevant portions of the specification referenced in the parenthesis:

> 16. A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell **{p. 5, ll. 23-28; p. 21, ll. 4-6}**, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made **{p. 6, ll. 4-5}**, wherein the neurovirulence of said herpes simplex virus is attenuated **{p. 5, ll. 7-8; p. 17, ll. 29-30}**.

Dependent claims 18-20 do not stand or fall with claim 16 because they benefit from separate grounds of patentability (see Section III of "Argument," *infra*). The subject matter of each of these claims is reproduced below, with parenthetical cross-references to the specification.

> 18. The herpes simplex virus of claim 16, further comprising at least one further gene alteration **{p. 6, ll. 6-7}**.

> 19. The herpes simplex virus of claim 18, wherein said at least one further gene alteration is in the ribonucleotide reductase gene, such that no functional ribonucleotide reductase is made **{p. 6, ll. 1-5}**.

> 20. The herpes simplex virus of claim 19, wherein said herpes simplex virus is G207 expressing the cytokine **{p. 21, ll. 4-6; p. 25, ll. 1-8}**.

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejections to be reviewed on appeal are:

(i) the rejection of claims 16, 28 and 29 under 35 U.S.C. 103(a) over U.S. Patent No. 6,172,047 to Roizman *et al.* ("Roizman") in view of Vile *et al., Ann. Oncol.* 5 Suppl. 4: 59-65 (1994) ("Vile");

(ii) the rejection of claims 18-20 under 35 U.S.C. 103(a) over Roizman in view of Vile, and further in view of Chang *et al., Virology* 185(1): 437-440 (1991) ("Chang"); and

(iii) the rejection of claims 30-32 under 35 U.S.C. 103(a) over Roizman in view of Vile, and further in view of WO 92/14821 by McKay *et al.* ("McKay") and U.S. Patent No. 5,639,656 to Wright, Jr. ("Wright").

## ARGUMENT

### I. Introduction

Needless to say, there has been a long-felt need for cancer treatment. The claimed invention addresses this need by providing an oncolytic herpes simplex virus (HSV) vector for use in treating cancer. The claimed invention thus sounds in oncolytic virotherapeutics, which is focused on providing an effective alternative to chemotherapy. See Loe, "Opinion: Can viruses kill cancer?" available at http://www.the-scientist.com/news/display/579170, 19 January 2011 ("One approach that has proven quite promising in clinical studies is known as oncolytic virotherapeutics . . . . [In this field] viruses are harnessed to infect, multiply within, and subsequently lyse cancer cells – all without affecting normal tissue").

When the present case was filed, those working in the then-nascent field of oncolytic virotherapeutics were disincentivized from combining, in an HSV vector, oncolytic activity with cytokine-expressibility, both of which are features of appellants' claimed invention. This is so because the contemporaneous HSV literature taught that the presence of cytokines *in situ* would counter or decrease HSV infectivity, an effect antithetical to the operation of an oncolytic-HSV therapeutic. See response filed on July 20, 2009, at page 5, last paragraph; response filed on December 18, 2008, at page 7; the response filed on May 14, 2008, at page 7, and the Rabkin declaration, submitted on May 14, 2008, at paragraphs 4 and 5.

On the strength of a hindsight-informed combination of disparate teachings about oncolytic therapy on one hand and cytokine expression on the other, Examiner Shen has dismissed evidence, including attestations by a recognized expert who worked in the field at the time, that is probative of the foregoing characterization of the state of the relevant art. The examiner thus committed reversible errors of law and fact to maintain the appealed rejections. These errors included: (i) downplaying or ignoring the substantial, *a priori* unpredictability endemic to oncolytic virotherapeutics, *circa* mid-1994, in order to effect a pseudo-mathematical "additive" combining of prior-art teachings, thereby arriving *post hoc* at the claimed invention;

(ii) substituting his judgment without valid basis for the principled attestations of a declarant dully qualified as an expert in the field; and (iii) discounting the declaration evidence of record by improperly asserting that it was not commensurate in scope with any appealed claim.

## II. Rejection over Roizman and Vile

### A. The skilled artisan would have been disincentivized from combining the vector-design elements of oncolytic activity and cytokine expression

In the prior art, the endeavors of HSV vector administration and cytokine expression belonged to different therapeutic domains, oncolytic viral therapy and cytokine gene therapy, respectively. See response filed on December 18, 2008, at pages 5 and 6. When the present application was filed, one skilled in the art would have been directed away from affecting the design of an HSV vector, a modality of virus-mediated oncolytic therapy, with an element of classical gene therapy, the heterologous expression of a cytokine.

This was the case because oncolytic therapy entails killing host cells by means of a replicating virus, such as an HSV vector, to lyse the cells. On the other hand, long-lasting expression of a cytokine gene and concomitant elicitation of an immune response in the host cells require that the host cells remain intact during expression. Therefore, the skilled artisan would not have combined a modality of oncolytic therapy, which aimed at killing host cells *in vivo*, with cytokine expression, which the prior art advanced as a therapeutic goal unto itself.

As evidenced by paragraph 4 of the Rabkin declaration, moreover, the contemporaneous art demonstrated that cytokines would protect a host from HSV infection and prevent HSV replication in the host. Therefore, it would have been the understanding of the skilled artisan that cytokine expression, *per se*, would counteract oncolytic therapy, which requires the HSV vector to infect and replicate serially in host cells.

In this regard, the examiner has responded to appellants' stated position and validating evidence by asserting that (i) "eliciting an immune response against a tumor cell" is considered as "inherent" properties of the cytokine (final Office action dated May 26, 2010, paragraph

bridging pages 3 and 4); (ii) the recited feature is an "intended use" and, hence, undeserving of "patentable weight" in determining the patentability of a product claim (*id.*, paragraph bridging pages 11 and 12); and (iii) there is no contradiction between the goals of gene therapy, evidenced by Vile, and oncolytic therapy per Roizman (*id.*, paragraph bridging pages 8 and 9). So doing, the examiner committed a number of errors, any one of which justifies reversal of the appealed rejections.

**First**, the examiner improperly invoked "inherency" to substantiate the rejection. Appellants have never denied that cytokines have the property of eliciting an immune response. Still, the examiner has invoked the notion "inherency" here in isolation, *i.e.*, with reference to the cytokine alone rather than to the context of the claimed invention. Consequently, the examiner's analysis downplayed the key issue of whether the skilled artisan would have introduced cytokine expression into the design of an oncolytic HSV vector, notwithstanding the *a priori* unpredictability of the field at the time and the potentially confounding (anti-infective) impact of such cytokine expression.

**Second**, the recited feature of eliciting an immune response should not be mislabeled as an "intended use," denying it patentable weight. Rather, the claim recitation in question sets forth a property or feature of appellants' invention, namely, the capability of eliciting an immune response against tumor cells. The examiner cites no valid basis for refusing patentable weight to the recitation, regardless of the type of claim.

**Third**, the posited combination of the cited art cannot be justified, as the examiner has, on the pseudo-mathematical basis of "1+1=2" additivity. The examiner asserts, because cancer treatment is a goal both of the gene therapy represented by Vile ("1") and of the oncoloytic therapy represented by Roizman ("1"), that it thus would have been obvious to combine features drawn from the respective therapies, apparently for some additive effect on anti-cancer efficacy ("1+1=2"). See final Office Action, the paragraph bridging pages 8 and 9.

So general a commonality of ***goal*** obscures the fact, however, that appellants' claimed invention embodies a vector design that flew in the face of a perceived contradiction of ***mechanism***, discussed above. That is, cytokine protection host from HSV infection would have led one of ordinary skill in the art away from combining, in an HSV vector, the features of oncolysis and cytokine expression (see Rabkin declaration, paragraphs 4 and 5).

**B. The examiner erroneously downplayed *a priori* unpredictability in the relevant field and instead imposed an *a posterori* "additivity" to justify combining otherwise disparate teachings on oncolytic therapy and on cytokine expression, respectively**

The nascent field of oncolytic virotherapeutics afforded the skilled artisan little or no guidance on balancing variables that could affect oncolytic efficacy. An effective oncolytic viral therapy requires both the initial invasion and replication thereafter of the HSV vector in the host cells; whereas cytokines were known to block infection and replication of HSV. See the response filed March 12, 2010, at page 4, last paragraph.

In contravention of conventional wisdom in the field, appellants introduced a potentially confounding factor, cytokine expression, which was known to protect host infection from HSV, into the regime of HSV oncolytic therapy. In fact, the 1994 Vile reference of record, which was published around the priority date of appellants' application, explicitly acknowledges that "such in situ gene therapy [as described by Vile] would require a specificity of gene delivery that is impossible using currently available viral vectors or physical transfer techniques" (page S59, left column, lines 12-15, under the heading "Introduction"),

At the time of appellants' invention, the skilled artisan in this new field would have received insubstantial guidance, if any, from the art on balancing the largely uncharacterized variables of vector design to achieve both oncolytic and cytokine efficacy. Accordingly, there would have been no principled way of predicting *a priori* the outcome, in terms of cancer treatment, of combining the presently recited features, drawn from oncolytic therapy and gene therapy (cytokine expression). By way of illustration in this regard, appellants enumerated the

following scenarios to show what the skilled artisan would have had to consider, in principle, without basis in any previous experience or demonstrated principle:

(a) if the expression of cytokine elicits an immune response that eliminates the HSV-infected host cells before HSV accomplishes the oncolytic effects, the net effect of the combined therapy is nothing more than the cytokine efficacy;
(b) if the replication of HSV kills the host cells before a sufficient amount of cytokine is expressed, the only benefit achieved is the oncolytic viral therapy; and
(c) if the replication of HSV parallels the immune response caused by the cytokine expression, the HSV is able to spread in tumor cells while the cytokine eliciting an anti-tumor immune response.

In circumstances of essential unpredictability, therefore, one of ordinary skill would have had no insight or grounds for expectation regarding possible outcome(s) from the combination of heretofore unrelated principles of virus-mediated oncolysis and cytokine expression. Acknowledging the lack of reasonable, *a priori* predictability in the prior art, the examiner nevertheless insisted that "a skilled person in the art would [have been] motivated to make the claimed HSV based on the combined references and to test how effective the claimed HSV may be in cancer gene therapy" (final Office Action at page 23, last line, through page 24, line 4). This conclusory statement simply does not answer on the point at bar. In the absence of any reasonable predictability and in view of the contravening teachings in the prior art, appellants have established that motivation was lacking to have combined the cited references. Even while agreeing that *a priori* predictability was lacking, the examiner has articulated no plausible rationale for insisting that motivation was evidenced for combining the references.

Accordingly, the examiner erred in maintaining the obviousness rejections without having sustained the Office's burden to establishing a *prima facie* case under Section 103.

**C. The examiner improperly dismissed the declaration evidence proffered in rebuttal of the examiner's obviousness rationale**

Appellants submitted the Rabkin declaration in part to substantiate the fact that one of ordinary skill would have been discouraged from combining the cited references as the examiner has posited, given the known, counteracting effects of cytokine expression on the HSV oncolytic activity (see above). Examiner Shen discounted the declaration evidence, however, (i) by substituting his own judgment, without basis, for an expert's opinion and (ii) by asserting that the declaration evidence is not commensurate in scope with the claimed invention.

**(i) The examiner's impression should not outweigh the declarant's averment**

Despite the declaration evidence, the examiner found no impediment in the art to combining disparate elements drawn from gene therapy and oncolytic therapy because "[t]here is no contradiction for the goal . . . of cancer treatment . . . to ultimately kill cancer cells without harming normal cells" (final Office Action at page 9, lines 3-5). Yet, the examiner has said nothing about the declarant's attestations concerning an art-recognized contradiction in ***mechanism***. See Rabkin declaration at paragraph 4. Again, the examiner's analysis improperly downplayed or ignored the impact of a contradiction perceived in the art, prior to appellants' invention, between the host cell-protective effect of cytokine expression and the serial infection/lysis of host cells, which is essential to the efficacy of an oncolytic HSV vector as claimed.

Instead, the examiner has interposed what he views as a "key issue regarding the time point when the cytokine gene is expressed from HSV (e.g. early gene versus late gene expression)," which, according to the examiner, "would affect the role of expressed cytokine." Final Office Action, page 20, 1st full paragraph.

Appellants would emphasize, however, that the cytokine-encoding "nucleotide sequence" of appealed claim 16 is foreign to and, hence, must be introduced into the recited HSV "genome." It is a *non sequitur*, therefore, to treat the cytokine-encoding nucleotide

sequence along the same timeline of endemic (viral) genes, which are characterized as "early" or "late" by reference to the timing of their expression.

Furthermore, the examiner's mere impression of a "key issue," so-called without foundation in any citation of record or, indeed, any well-reasoned rationale, cannot be so compelling as to negate Declarant Rabkin's testimony that "the claimed invention requires a cytokine-expressing HSV to infect and replicate in tumor cells, thereby to elicit an anti-tumor immune response, and yet the contemporaneous literature . . . indicated that the cytokines would counter or decrease the prerequisite HSV infection and replication." In point of evidenced fact, therefore, the declarant's characterization of "the contemporaneous literature," like his other attestations, stands unrebutted on the present record.

**(ii) The declaration evidence is commensurate in scope with the claimed invention because the skilled artisan would have recognized a reasonable correlation between the claimed HSV vector and the HSV vectors encompassed by the declaration**

As set forth in *M.P.E.P.* § 2145, "commensurate in scope" does not mean "exactly identical." Rather, an evidentiary showing and a claim are proportionate or commensurate in scope when "a reasonable correlation [exists] between the showing and the entire scope of the claim, when viewed by a skilled artisan." *Id.*

In *In re Cescon*, 474 F.2d 1331 (C.C.P.A. 1973), the PTO's reviewing court reversed a board's adverse ruling on "the sufficiency of the evidence presented in appellant's specification to support the alleged interrelationship of ortho substitution," for a broad category of claimed imidazolyl dimer compounds, and certain "improved properties," which the appellant had invoked to substantiate non-obviousness for the category. 474 F.2d at 1334. In particular, the court voiced its "disagreement with … overly stringent standards set up" by the PTO "for evaluating appellant's objective evidence." *Id.*.

> *It is true that the claims are broadly drawn to the presence of imidazolyls in the environment of an inert solvent or substrate. The examples providing*

> *comparisons with analogously substituted isomers or unsubstituted imdazoles, on the other hand, are limited to the use of a benzene solution. Not all compounds encompassed by the claims are tested. But ample data has [sic] been provided to establish the correlation between ortho substitution on the 2-phenyl ring and greatly increased color fading rates. Moreover, no factual basis appears in the record for expecting the compounds to behave differently in other environments. Therefore, we reverse the 103 rejection.*

*Id.* (emphasis added). *Cf. In re Glatt Air Techniques Inc.*, No. 2010-1141, 2011 U.S. App. LEXIS 79, at *11 (Fed. Cir. January 5, 2011) (court reverses PTO finding that evidence rebutting obviousness was not commensurate in scope with disputed claim 5, noting that, "[t]o the extent the PTO asserts that Glatt needed to submit commercial success evidence from multiple embodiments for that evidence to be commensurate in scope with claim 5, this position is not consistent with our precedent").

On two occasions the examiner asserted that appellants' rebuttal evidence is not commensurate in scope with the claims. In one instance, the examiner contends that Exhibits A, C, F and H accompanying Rabkin's declaration and the publication by Ghiasi (submitted on July 20, 2009) are not commensurate in scope with the claims because the HSV vectors illustrated by Exhibits A, C, F and H do not have the same null mutations of γ34.5 and ribonucleotide reductase. See final action, the paragraph bridging pages 12 and 13. In terms of Ghiasi, the examiner further asserted that "the claimed HSV [is] already non-pathogenic/virulent due to the presence of γ34.5 mutation" (*id*).

Although the claimed HSV vector is attenuated for its virulence, it still is required to be replication-competent in dividing cells, *e.g.*, cancer cells. Therefore, as evidenced by Exhibits A, C, F and H, as well as by Ghiasi, showing that cytokine expression blocks infection and replication of HSV, the skilled artisan reasonably would have made a correlation with the claimed HSV vector, based on the common feature of "replication-competence," and hence would have anticipated that cytokine expression likewise would have blocked the replication of the claimed HSV vector in dividing cells.

On the other occasion, the examiner contended that evidence proffered on the NV1042 vector illustrated in Liu's publication (submitted on July 20, 2009) is not commensurate in scope with the claimed invention. See, in the final action, the paragraph bridging pages 16 and 17. There is no factual basis in the present record, however, for the examiner to label the γ34.5 mutation as "the most critical element" (see below) and to eschew, in this context, the common feature shared by the HSV vectors. In the response filed on March 12, 2010, appellants urged that their rebuttal evidence is commensurate with the claimed invention because the HSV mutants exemplified by the cited publications are in the same category of HSV vectors delineated by the claims, *i.e.*, the category of replication-competent, oncolytic HSV vectors. Thus, the skilled artisan would have understood that the HSV vector of Liu is reasonably correlated with the claimed HSV vector because both are attenuated, replication-competent, oncolytic HSV vectors.

The above-identified correlation in turn underpins and substantiates Rabkin's testimony, otherwise unrebutted on the record, that the skilled artisan would not have expressed a cytokine in an oncolytic HSV vector due to the protective effects of cytokine on host cells from HSV infection and replication.

Nevertheless, the examiner asserts that "it is crystal clear that the specific 'gamma 34.5 mutation', which renders the HSV non-pathogenic and virus cannot replicate and spread, is the MOST CRITICAL element of [the] claimed products" (final Office Action at page 22, 1st full paragraph). Despite his express acknowledgement of the features of the claimed HSV vector, namely, attenuated (or "non-pathogenic") character and replication-competence (capability to replicate in dividing cells but not in normal cells), the examiner has refused to recognize that these features are shared by the HSV vector of Liu. Again, the examiner ignored an expert's averment on how these HSV vectors would have been viewed by a skilled artisan, before the invention was made, and relied instead on his personal judgment, unsupported on the record, that the specific γ34.5 mutation is the "most critical" element of the claimed invention. Accordingly,

Examiner Shen's dismissal of the declaration evidence lacks valid factual basis and therefore and constitutes reversible error.

## III. Rejection over Roizman, Vile and Chang

Claims 18-20 do not stand or fall with claim 16 because they benefit from additional grounds of patentability due to the examiner's misinterpretation of Chang.

The teachings of Roizman and Vile are discussed above. Chang was originally cited for the alleged teaching of an HSV having a mutation in the ribonucleotide reductase gene. See final office action at page 26. In any event, however, the teaching of an additional mutation in the HSV vector could not compensate for the deficiencies of Roizman and Vile.

In the final office action, the examiner further cited Chang for the alleged teaching of "the introduction of a foreign gene (e.g. a cytokine gene taught by Vile et al.)." See page 8, lines 11-15. In fact, Change does not even hint at introduction of a cytokine gene. Rather, Chang describes knocking out ICP6 gene by a deletion of part of the ICP6 gene or by an in-frame insertion of a *lacZ* gene into the ICP6 gene. See the abstract and page 438, left column. Expression of a *lacZ* gene is quite different from expression of a cytokine gene. In the former instance the gene serves as an expression marker, with no known contradicting effects to the host cells. In the latter instance, by contrast, expression of a cytokine gene would have been deemed a confounding factor in the context of oncolytic therapy (see above). Accordingly, Chang adds no weight to the examiner's rejection rationale.

## IV. Rejection over Roizman, Vile, McKay and Wright

The teachings of Roizman and Vile are discussed above. McKay and Wright are cited for the alleged teaching of tumor-specific promoters. Yet, such teaching does not cure the above-discussed deficiencies of the primary reference and the secondary references, respectively.

## CONCLUSION

Appellants respectfully submit that the appealed grounds for the above-discussed rejection are not sustainable. Appellants therefore request that the Board reverse the rejections in whole and pass the appealed claims on to issuance.

Respectfully submitted,

Date January 27, 2011

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## APPENDIX A: CLAIMS INVOLVED IN APPEAL

1-15. (Cancelled)

16. (Previously Presented) A herpes simplex virus with a genome that comprises (i) an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response against a tumor cell, and (ii) an alteration in the γ34.5 gene such that no functional γ34.5 gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated.

17. (Cancelled)

18. (Previously Presented) The herpes simplex virus of claim 16, further comprising at least one further gene alteration.

19. (Previously Presented) The herpes simplex virus of claim 18, wherein said at least one further gene alteration is in the ribonucleotide reductase gene, such that no functional ribonucleotide reductase is made.

20. (Previously Presented) The herpes simplex virus of claim 19, wherein said herpes simplex virus is G207 expressing the cytokine.

21.-27. (Cancelled)

28. (Previously Presented) The herpes simplex virus of claim 16, wherein an essential viral gene product of said virus is under the control of a tumor cell-specific promoter rather than its own viral promoter.

29. (Previously Presented) A composition comprising the herpes simplex virus of claim 16 and a pharmaceutically acceptable vehicle for said virus.

30. (Previously Presented) The herpes simplex virus of claim 28, wherein said tumor cell-specific promoter is nestin promoter.

31. (Previously Presented) The herpes simplex virus of claim 28, wherein said tumor cell-specific promoter is basic fibroblast growth factor promoter.

32. (Previously Presented) The herpes simplex virus of claim 28, wherein said tumor cell-specific promoter is epidermal growth factor promoter.

## APPENDIX B: EVIDENCE

1. U.S. Patent No. 6,172,047 to Roizman *et al.*;
2. Vile *et al., Ann. Oncol.* 5 Suppl. 4: 59-65 (1994);
3. Chang *et al., Virology* 185(1): 437-440 (1991);
4. PCT Publication No. WO 92/14821 by McKay et al.;
5. U.S. Patent No. 5,639,656 to Wright, Jr.;
6. Ghiasi *et al., J. Virol.* 76: 9069-9078 (2002); and
7. Liu *et al., Cancer Res.* 65: 1532-1540 (2005)

## APPENDIX C: RELATED PROCEEDINGS

An appeal is pending in Application No. 11/097,391.